Marked up versions of Amended Claims

On page 7, see **Version with markings to show changes made.**

REMARKS

Claims 1, 3, 5-22 appear in this application. By this Amendment, Claim 12 is amended and claims 17-20 are cancelled without prejudice. Subsequent to this amendment, the still pending claims are 1, 3 and 5-16, 21-22.

Support for amended Claim 12

Support for amended Claim 12 to include the language "selected from the group consisting of" can be found in the specification (Page 7, lines 28-29) which indicates that Applicants did not intend that necessarily all of the specified biodegradable polymers be present in the matrix simultaneously.

Rejection based on failure to include an abstract under 37 CFR 1.72(b) (Page 2 of the Office Action)

Applicants have added an abstract to their application. The abstract is identical to that in the PCT application upon which the present application is based.

Rejection of Claims 12 and 13 under 35 U.S.C. 112 as being ind finite (Pag 2 of the Office Action)

The claims are rejected on the grounds that the term, "polymer matrix", does not have antecedent basis. In response Applicants have amended Claim 12.

Rejection of Claims 1, 3 and 5-22 under 35 U.S.C. 103(a) as being unpatentable over Sparks et al. (Page 3 of the Office Action)

This rejection is respectfully traversed.

Although Applicants' particles are significantly smaller than those of Sparks et al., they release their contents more slowly than those of Sparks et al. That property of Applicants' particles is not only beneficial from the point of view of a controlled release preparation, but also surprising.

Applicants' Claim 1 is for formulations with a D50% in the range 100 nm to 900 nm. That size limitation, or a narrower one, applies to all the other pending claims as they are dependent on Claim 1. In support, Applicants disclose data for particles within that nanometer range. In Example 9, Figures 5-7 show release from 20%, 30% and 50% diltiazem base-loaded nanospheres, respectively (See Page 32, lines 4-5). For those nanospheres, the D50% was 294.0 nm, 307.5 nm, and 310.0 nm, respectively. (See page 31, lines 23-26).

Sparks et al., in contrast, provide drug release data for particles with a size of 90 to 125 uM. (See Examples 1-10, especially col. 10, lines 54-57 and col. 11, lines17-18.)

Sparks et al. studied release of their particles in simulated intestinal fluid, excluding enzymes (col. 10, lines 7-12). The drug load was about 9% w/w (see col. 10,

lines 16-28). After 6 hours, the amount of release was in the range, 70% to 100%. After 8 hours, the amount of release was in the range, 78 - 100%.

Release from Applicants' nanometer particles was studied at 3 pH's including pH 1.2, that of simulated gastric fluid (i.e., simulated intestinal fluid). In two of the three cases at pH 1.2, corresponding to drug loads of 20% and 30% w/w, respectively, the percentage release at 6 hours was in the range 55-68% and at 8 hours and in the range 56 to 70% (Figs. 5 and 6). Because they reflect a release that is more extended over time, those release kinetics were superior to those of Sparks et al. Only when drug loads of 50% were used by Applicants (Fig. 7) , were the release kinetics inferior to those of Sparks et al.

Applicants' release kinetics are surprising because faster release is expected for smaller particles due to the fact that the drug molecules in a smaller particle, on the average, need to cover a smaller distance to reach the particle surface and escape the particle.

In summary, although Applicants' claimed particles are significantly smaller than those of Sparks et al., they surprisingly have slower, superior release kinetics than those of Sparks. This is beneficial from the point of view of controlled release kinetics. (It is also beneficial from the point of view that the smaller particles are more easily dispersed in solution, which provides a more pleasant experience for the person drinking the suspension.)

In view of the foregoing, allowance of all claims is requested.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

12 (Twice Amended). A pharmaceutical formulation of Claim 1, wherein the microcapsules comprise a polymer matrix [comprises] ,said polymer matrix comprising a polymer selected from the group consisting of polylactide[;], polyglycolide[;] poly(lactic acid-co-glycolic acid)[;], poly(e-caprolactone)[;], poly(hydroxybutyric acid)[;], polyortho-esters[;], polyacetals[;], polydihydropyrans[;], polycyanoacrylates[;], polypeptides[;], cross-linked polypeptides[;], and stereoisomers, racemic mixtures, co-polymers and polymer mixtures thereof.

CERTIFICATE OF MAILING

I hereby certify that the foregoing AMENDMENT and a Petition for Revival of AN Application, Transmittal Form, and a Fee Transmittal FY 2003, re Application Serial No. 08/722,045 are being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to: Assistant Commissioner for Patents, Box DAC, Washington, D.C. 20231 on this 13th day of November, 2002.

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Reg. No. 31,253